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(54) Injectable compositions containing Nimesulide

(57) Novel therapeutic anti-inflammatory and analgesic compositions are disclosed containing Nimesulide, i.e. N-(4-nitro, 2 phenoxyphenyl) methane sulphonamide for use intramuscularly, also a process for their preparation.

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Description

The present invention relates to a novel Therapeutic Injectable Analgesic pharmaceutical Composition containing Nimesulide which is N-(4-nitro, 2-phenoxyphenyl) methanesulfonamide, for intra-muscular administration and a process for the manufactur thereof.

BACKGROUND OF THE INVENTION

The use of Nimesulide through intra-muscular administration as an analgesic agent has not been successful because Nimesulide is practically insoluble in water and its formulations in conventional oily bases or as suspensions result in depot formation in the muscular tissues which defied the main objective of quick relief.

The market and literature surveys show that no parenteral dosage form of Nimesulide is reported. (Drugs, 48 (3) 431-454, 1994).

An injectable formulation of nimesulide has been reported in the prior art (PCT Patent No. WO 95/34533) which utilizes a salt form of nimesulide (nimesulide-L-lysine) complexed with cyclodextrins. The maximum solubility achieved was reported to be 2.4 mg/mL, which is not suitable for an intramusular injection as it would require very large volumes to administer therapeutic doses. The reported oral dose of nimesulide ranges between 100 to 400 mg per day. Contemplating that the intramuscular dose is half of the oral dose, 50 mg of the drug needs to be injected which would require approximately 20 ml of the solution described in the prior art i.e. WO 95/34533.

Whereas in the present invention we report an intramuscular injection formulation of nimesulide which incorporates the drug molecule in a suitable base having a concentration of 50 mg/ml. With this formulation therapeutically effective doses of nimesulide can be administered conveniently. Moreover, the present invention gives the flexibility of injecting 0.5 ml to 3.0 ml of the 50 mg/ml solution as per the dosage requirements.

The present invention utilizes solubilization techniques to achieve such high concentrations of nimesulide and no salt forms or complexing agents were used as reported previously.

It is an object of the present invention to provide a Novel Therapeutic Injectable Analgesic Composition containing Nimesulide for intra-muscular administration from which the Nimesulide is rapidly absorbed and distributed in body fluids.

It is a further object of the present invention to provide a process for the preparation of the novel Therapeutic Injectable Analgesic Composition containing Nimesulide, according to the present invention, for intramuscular administration.

SUMMARY OF THE INVENTION

The present invention provides a novel therapeutic Injectable Analgesic pharmaceutical Composition for intra-muscular administration which composition comprises :

Nimesulide
: 2.5% to 10% w/v
Parenteral absorption enhancing vehicle base
: 90% to 97.5% w/v

The said Parenteral absorption enhancing vehicle base comprises

Dimethylacetamide	: 5% to 12% w/v.
Benzyl benzoate	: 20% to 50% w/v.
Benzyl alcohol	: 0% to 10% w/v.
Ethyl oleate	: 30% to 65% w/v.

According to a preferred embodiment of the present invention, the novel Therapeutic Injectable Analgesic Composition Comprises :

Nimesulide	: 5% w/v.
Dimethylacetamide	: 10% w/v.
Benzyl benzoate	: 40% w/v.
Benzyl alcohol	: 2% w/v.
Ethyl oleate	: 30% to 65% w/v.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel therapeutic Injectable Analgesic pharmaceutical Composition for intra-muscular administration which composition comprises :

Nimesulide
: 2.5% to 10% w/v
Parenteral absorption enhancing vehicle base
: 90% to 97.5% w/v

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Benzyl alcohol	: 0% to 10% w/v.
Ethyl oleate	: 30% to 65% w/v.

According to a preferred embodiment of the present invention, the novel Therapeutic Injectable Analgesic Composition Comprises :

Nimesulide	: 5% w/v.
Dimethylacetamide	: 10% w/v.
Benzyl benzoate	: 40% w/v.
Benzyl alcohol	: 2% w/v.
Ethyl oleate	: 30% to 65% w/v.

According to another pref rred mbodiment of the present inv ntion, th Benzyl benzoate used is replaced

in part by 5% to 10% w/v of Cremophors (Polyoxyethylene glycolated castor oils)EL.

According to another preferred embodiment of the present invention, a conventionally known anti-oxidant such as ascorbyl palmitate, butyl hydroxy anisole, butyl hydroxy toluene, propyl gallate and α-tocopherol is added to the said Injectable analgesic composition.

The present invention also provides a process for the preparation of the novel Therapeutic Injectable Analgesic Composition, according to the present invention, which process comprises the following steps:

(a) 5% to 12% w/v of Dimethylacetamide and 20% to 50% w/v of Benzyl benzoate are mixed in a container fitted with a Stirrer at slow speed (1000-1500 rpm) and to that 3% to 7% w/v of Nimesulide is added and stirred till completely dissolved.
(b) 0% to 10% w/v of Benzyl alcohol and a portion of 30% to 65% w/v of Ethyl oleate are mixed in a container fitted with a stirrer.
(c) The mixture obtained in step (a) is added to the mixture obtained in step (b) under slow stirring and the volume of the mixture obtained is made upto 100 ml by the rest of the amount of Ethyl Oleate resulting in the preparation of the desired Injectable analgesic Composition.

According to a preferred embodiment of the Process according to the present invention, in the step (a) of the said process 10% w/v of Dimethylacetamide and 40% w/v of Benzyl benzoate are mixed and to that 5% w/v of Nimesulide are added. In the step (b) of the said process, 2% w/v of Benzyl alcohol and a portion of 30% to 65% w/v of Ethyl oleate are mixed.

Preferably the step (c) of the said process is carried out under continuous nitrogen flushing and the resulting solution obtained is passed through 0.22 μ nylon membrane filter.

According to another preferred embodiment, of the present invention, a conventionally known anti-oxidant such as ascorbyl palmitate, butyl hydroxy anisole, butyl hydroxy toluene, propyl gallate and α-tocopherol is added to the said Injectable analgesic composition, as prepared.

The present invention is exemplified by the following examples for the preparation of the Injectable Analgesic composition.

Example I

(a) Mix 10 g of Dimethylacetamide and 40 g of Benzyl benzoate in a container fitted with a stirrer at slow speed (1000-1200 rpm) at a temperature between 25°-30°. Add 5 g of Nimesulide in small increments and stir till completely dissolved.
(b) Mix 10 g of Cremophor EL and an amount of Ethyl oleate in a container fitted with a stirrer at room temperature.
(c) Add the mixture obtained in step (a) to the mixture obtained in step (b) under slow stirring and stir for about 30 minutes. Make up the volume to 100 ml with Ethyl oleate and filter through 0.22 μ nylon membrane filter to make it sterile.

Example II

(a) Mix 20 g of Dimethylacetamide and 76 g of Benzyl benzoate in a container fitted with a stirrer at slow speed at a temperature between 25°-30°C. Add to the mixture obtained 10 g of Nimesulide in small amounts at a time and stirred till completely dissolved.
(b) Mix 4 g of Benzyl alcohol and an amount of Ethyl oleate in a container fitted with a stirrer at room temperature.
(c) Add the mixture obtained in step (a) to the mixture obtained in step (b) under slow stirring and stir for about 30 minutes. Make up the volume to 200 ml with Ethyl oleate and filter through 0.22 μ nylon membrane filter to make it sterile.

The Injectable Analgesic composition, according to the present invention, on preliminary animal and preclinical trials has been shown to possess marked analgesic activity. Further it has been found to be non-toxic even on repeated applications at the same site. No incidence of tissue necrosis or any other side effect was observed. The analgesic dose ranges from 0/16 mg/kg to 8.4 mg/kg. This analgesic composition is very effective and useful for the treatment of acute painful conditions like post-operative trauma, pain associated with cancer, sports injuries and the like.

The analgesic activity of the therapeutic composition, prepared according to the present invention, was found to be dose dependent and passed the tests of subacute toxicity and undue toxicity.

The preclinical toxicology studies showed values at LD_{50} =129.55 mg/kg, ED_{50} =3 mg/kg with a therapeutic index = 43.13 in mice. This demonstrates high safety of the present invention.

The therapeutic Injectable Analgesic Composition, according to the present invention, is not a mere admixture but has properties different from the sum total of the properties of its ingredients, as stated herein above.

Since many apparently different embodiments of the present invention could be made without departing from the spirit and scope thereof, it is intended that the description of the invention herein be interpreted as being illustrative only and not limiting in any manner whatsoever.

Claims

1. A Therapeutic Injectable analgesic pharmaceutical Composition for intra-muscular administration comprising the following ingredients :

   Nimesulide

: 2.5% to 10% w/v

Parenteral absorption enhancing vehicle base
: 90% to 97.5% w/v

2. A pharmaceutical injectable Composition as claimed in claim 1 wherein said parenteral absorption enhancing base comprises:

Dimethylacetamide	: 5% to 12% w/v
Benzyl benzoate	: 20% to 50% w/v
Benzyl alcohol	: 0% to 10% w/v
Ethyl oleate	: 30% to 65% w/v

3. A pharmaceutical injectable Composition as claimed in claim 2 which preferably comprises the following ingredients :

Dimethylacetamide	: 10% w/v
Benzyl benzoate	: 40% w/v
Benzyl alcohol	: 2% w/v
Ethyl oleate	: 30% to 65% w/v

4. A pharmaceutical Composition as claimed in Claim 3 wherein the Benzyl benzoate used is replaced in part by 5% to 10% w/v of Cremophor EL.

5. A pharmaceutical Composition as claimed in Claim 1 wherein a conventionally known anti-oxidant, as herein described, is added to the Composition.

6. A process for the preparation of novel Therapeutic Injectable Analgesic Composition containing Nimesulide for intra-muscular administration which comprises the following steps :

(a) mixing 5% to 12% w/v of Dimethylacetamide and 20% to 50% w/v of Benzyl benzoate in a container and adding thereto 3% to 7% w/v of Nimesulide and stirring till completely dissolved.

(b) mixing separately 0% to 10% w/v of Benzyl alcohol and a portion of 30% to 65% w/v of Ethyl oleate;

(c) adding the mixture obtained in step (a) to the mixture obtained in step (b) under slow stirring resulting in the preparation of the desired Injectable Analgesic Composition.

7. The process as claimed in claim 6 wherein in step (a) 10% w/v of Dimethylacetamide and 40% w/v of Benzyl benzoate are mixed and to that is added 5% w/v of Nimesulide.

8. The process as claimed in claim 6 where in step (b) 2% w/v of Benzyl alcohol and a portion of 30% to 65% w/v of ethyl oleate are mixed.

9. The process as claimed in claim 6 wherein the Benzyl benzoate used in step (a) is replaced in part by 5% to 10% w/v of Cremophor EL.

10. The process as claimed in claim 6 wherein a conventionally known anti-oxidant, as herein described, is added to the Injectable Analgesic Composition as prepared.

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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 4461

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	WO 95 34533 A (EUROPHARMACEUTICALS SA ;PIROTTE BERNARD (BE); PIEL GERALDINE (BE);) 21 December 1995 * page 1, line 16 - line 25 * * page 10; table 1 * * page 13, line 13 - line 18 * * page 14, line 33 - line 34 * * page 23; example 16 *	1	A61K31/63
A	WO 94 28031 A (CYCLOLAB LTD ;EUROPHARMACEUTICALS SA (BE); GECZY JOSEPH (BE)) 8 December 1994 * page 6, line 1 - line 4 * * page 13; example 15 *	1	
A	US 3 840 597 A (MOORE G ET AL) 8 October 1974 * column 6, line 34 - line 39 *	1	
A	DRUG DEV. IND. PHARM., vol. 20, no. 17, 1994, pages 2753-2762, XP002019928 RADWAN M. ET AL: "In Vivo Screening Model for Excipients and Vehicles used in Subcutaneous Injections" * page 2755; table 1 *	1-5	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	5 December 1996	Boulois, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
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